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CONJUGATE ADDITION REACTION OF INDOLE TO PROTECTED 2-AMINO-1-NITROETHENES MEDIATED BY SILICA GEL

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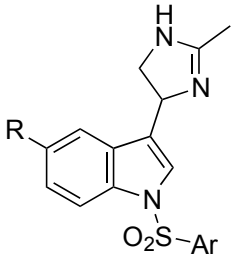
Abstract – We have developed a silica-gel-mediated route for the conjugate addition of indole to protected 2-amino-1-nitroethenes for the synthesis of 1-indolyl-1,2-ethanediamines. This is the first demonstration of indole as the nucleophile for addition to protected 2-amino-1-nitroethenes.

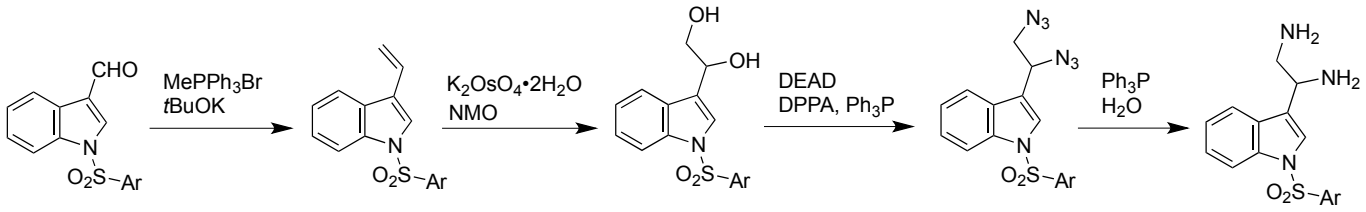
We have recently studied novel kallikrein 7 (KLK7, a stratum corneum chymotryptic enzyme) inhibitors and found that a series of imidazolinylindole derivatives **1** showed potent inhibitory activities (Figure 1).[1] To perform structure–activity relationship studies, we prepared imidazolinylindole derivatives from indolyl diamines, which were synthesized from indolyl aldehyde by the general route shown in Scheme 1. The route involves Wittig olefination of 1-(arylsulfonyl)indole-3-carboxaldehyde with methyltriphenylphosphonium bromide, dihydroxylation of the alkene with $K_2OsO_4 \cdot 2H_2O$ and *N*-methylmorpholine oxide (NMO), azidation using a Mitsunobu reaction with diphenylphosphoryl azide (DPPA), and Staudinger reduction of the azides.[2] Although the synthesis itself is robust, the problem with this route is that it involves diazides, which are potentially explosive and considered to be an obstacle for future large-scale synthesis. Therefore, we focused on developing a safer synthetic route for indolyl diamines without using azide compounds.



1 R = H, Me, Br

Figure 1. Chemical structure of KLK7 inhibitor developed by us

This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.



Scheme 1. Previous synthesis of 1-indolyl-1,2-ethanediamine

Due to the importance of the 1,2-diamino motif in synthetic and pharmacological chemistry, diamine synthetic methods have been actively studied in organic chemistry.[3,4] Recently, methods using nucleophilic addition to protected 2-amino-1-nitroethenes to access 1,2-diamino motifs have been reported by several groups (Figure 2).[5] These methods are attractive because the unit leading to diamino functionality can be introduced immediately without the use of azides or an olefin precursor. Until now, the reported nucleophiles have been limited to enolizable carbonyl compounds such as aldehydes, ketones, and oxindoles, while no use of an indole has been reported as a nucleophile for addition to protected 2-amino-1-nitroethenes. However, considering the nucleophilicity of indoles and the reported nucleophilic addition of indoles to β-aryl- or alkyl-substituted nitroolefins,[6] we assumed that indoles could be used for this addition reaction.

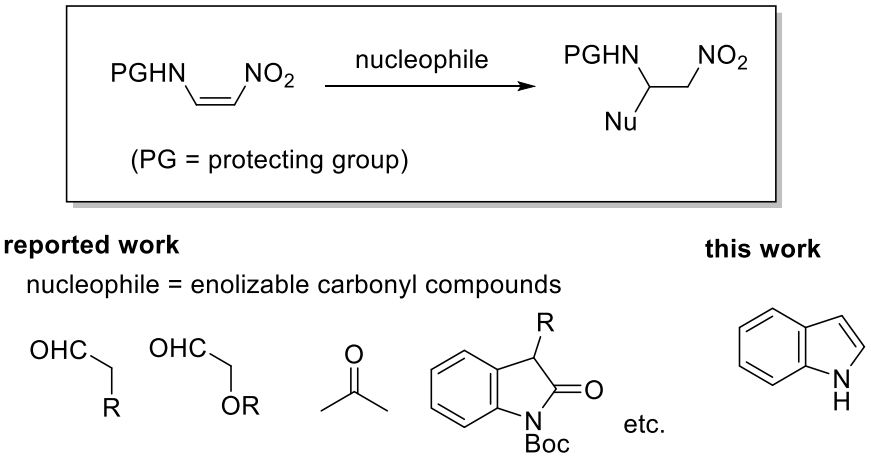
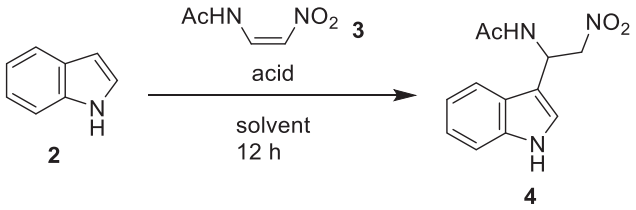


Figure 2. Nucleophilic addition to protected 2-amino-1-nitroethenes

To test the feasibility of this proposition, the reaction between indole (**2**) and Ac-protected 2-amino-1-nitroethene **3** was examined.[7] Compound **3** was readily prepared by a reported method.[5a] Among various acids reported for conjugate additions to nitroolefins, we focused on silica gel to promote the reaction.[8] This is because silica gel is a mild acid and easy to handle, and the reaction can be conducted under metal-free conditions. The reaction in the presence of silica gel in dichloromethane was first examined, but the desired addition hardly proceeded (Table 1, entry 1). The reaction under

solvent-free conditions was then examined as follows: compounds **2** and **3** were dissolved in dichloromethane, silica gel was added to the solution, the solvent was removed under reduced pressure, and the resulting silica gel with adsorbed organic compounds was stirred. When the reaction was carried out at room temperature, only a trace amount of the desired product was obtained (entry 2). On the other hand, the reaction proceeded successfully when carried out at 60 °C. The desired adduct **4** was obtained at 92% yield in 12 h (entry 3). As a result, the reaction conditions for the addition of indole to the protected 2-amino-1-nitroethene were established. It should be noted that the use of $Cu(OTf)_2$, $Zn(OTf)_2$, or $PhCO_2H$ in dichloromethane instead of silica gel was not effective (entries 4–6).

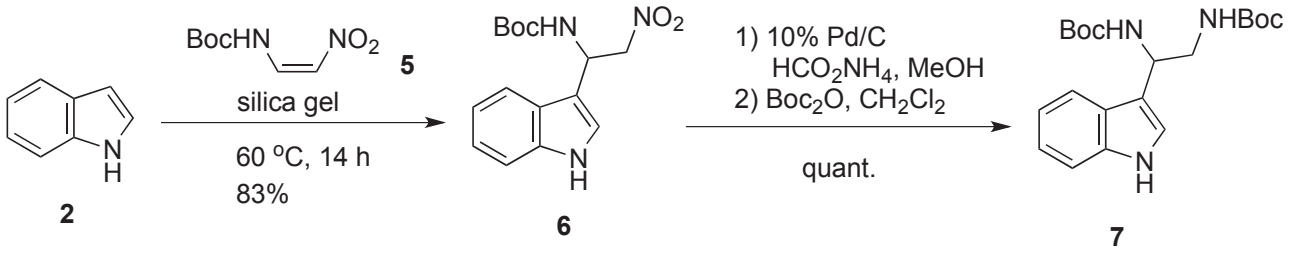
Table 1. Screening of reaction conditions



entry	acid	solvent	temp.	result
1	SiO_2 [a] (20 wt%)	CH_2Cl_2 [b]	rt	trace
2	SiO_2 [a] (500 wt%)	none	rt	trace
3	SiO_2 [a] (1000 wt%)	none	60 °C	92%
4	$Cu(OTf)_2$ (10 mol%)	CH_2Cl_2 [b]	rt	trace
5	$Zn(OTf)_2$ (10 mol%)	CH_2Cl_2 [b]	rt	trace
6	$PhCO_2H$ (20 mol%)	CH_2Cl_2 [b]	rt	trace

[a]MERCK silica gel 60 (230–400 mesh). [b]0.2 M

With compound **4** in hand, we initially attempted direct conversion to 2-methylimidazoline via reduction of the nitro groups and subsequent intramolecular cyclization.[9] However, this attempt was unsuccessful. Therefore, we next attempted to synthesize indolyl diamines. For this purpose, we planned to use 2-amino-1-nitroethenes with a protecting group that is more easily removed than acetyl. Taking into account that Boc groups could be easily removed under acidic conditions, Boc-protected 2-amino-1-nitroethene **5**[5b] was applied (Scheme 2). Under the selected conditions, the reaction between compound **5** and indole (**2**) proceeded to give desired adduct **6** in 83% yield. The nitro group in adduct **6** was reduced using Pd/C and ammonium formate, and the resulting amine was treated with Boc_2O to give Boc-protected indolyl diamine **7** quantitatively. This compound is a useful intermediate that could be used in the synthesis of various imidazolinylindole derivatives, and thus we have achieved the diazide-free synthesis of 1-indolyl-1,2-ethanediamine.



Scheme 2. Synthesis of Boc-protected indolyl diamine **7**

In summary, we have developed a route for the conjugate addition of indole to protected 2-amino-1-nitroethenes for the synthesis of 1-indolyl-1,2-ethanediamines. For the reaction, solvent-free conditions using silica gel are optimal. We have demonstrated that the adduct was easily converted to Boc-protected 1-indolyl-1,2-ethanediamine, which is expected to be useful for the synthesis of imidazolinylindole derivatives. To the best of our knowledge, this is the first report of the conjugate addition of indole to protected 2-amino-1-nitroethenes. Studies on applications of this reaction, including an asymmetric reaction, are currently underway.

EXPERIMENTAL

General Information

^{1}H-NMR and ^{13}C-NMR spectra were measured on JEOL JNM-ECS 400 and JEOL ECS 300 spectrometers, respectively, with tetramethylsilane as an internal standard. IR spectra were recorded on a Shimadzu FTIR 8400 spectrometer. High-resolution mass spectra and elemental analysis were performed by the Elemental Analysis Section of Osaka University. Column chromatography was performed with SiO_2 (Merck Silica Gel 60, 230–400 mesh). Unless otherwise noted, materials were purchased from Aldrich, Tokyo Chemical Industry, Kanto Kagaku, Wako Chemicals, and other commercial suppliers and were used without purification.

Compound 4

To a solution of indole (**2**) (54.0 mg, 0.461 mmol) and compound **3** (60.0 mg, 0.461 mmol) in CH_2Cl_2 was added silica gel (600 mg), and the solvent was removed under reduced pressure. The residual silica gel was stirred at 60 °C for 14 h. After cooling to room temperature, the resulting silica gel was loaded onto a silica-gel column. Chromatographic separation was carried out using hexane–AcOEt (1:1) to furnish compound **4** (104.7 mg, 92%) as a yellow solid.

Mp 156–159 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.37–7.12 (m, 4H), 6.43 (d, *J* = 6.9 Hz, 1H), 5.96 (d, *J* = 6.4 Hz, 1H), 4.95–4.79 (m, 2H), 1.97 ppm (s, 3H); ^{13}C-NMR (75.5 MHz, $(CD_3)_2CO$): δ = 170.0, 137.6, 126.7, 123.6, 122.8, 120.2, 119.5, 112.7, 112.4, 78.7, 45.6, 22.8

ppm; IR (KBr): 3408, 3304, 3057, 2929, 1645, 1552, 1460, 1427, 1381, 1338, 1278, 1101, 1041, 1010 cm^{-1}; HRMS (MALDI-TOF): calcd for $C_{12}H_{13}N_3O_4Na$ $[M+Na]^+$: 270.08491, found 270.08480.

Compound 6

To a solution of indole (**2**) (101 mg, 0.87 mmol) and compound **5** (180 mg, 0.95 mmol) in CH_2Cl_2 was added silica gel (900 mg), and the solvent was removed under reduced pressure. The residual silica gel was stirred at 60 °C for 12 h. After cooling to room temperature, the resulting silica gel was loaded onto a silica-gel column. Chromatographic separation was carried out using hexane–AcOEt (1:1) to furnish compound **6** (219.8 mg, 83%) as a pale-orange oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.42 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.38–7.09 (m, 4H), 5.70 (q, *J* = 6.9 Hz, 1H), 5.22 (brs, 1H), 4.96 (brs, 1H), 4.84–4.80 (m, 1H), 1.46 ppm (s, 9H); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 136.4, 123.0, 122.5, 122.2, 120.4, 119.8, 119.0, 118.5, 111.7, 111.5, 60.4, 28.0, 14.2 ppm; IR (KBr): 3408, 2980, 1691, 1552, 1492, 1460, 1425, 1367, 1247, 1166, 1107, 1051, 1022 cm^{-1}; HRMS (MALDI-TOF): calcd for $C_{15}H_{19}N_3O_4Na$ $[M+Na]^+$: 328.12678, found 328.12721.

Compound 7

To a solution of compound **6** (213 mg, 0.70 mmol) in MeOH (3.5 mL) were added 10% Pd/C (50 mg) and ammonium formate (440 mg, 7.0 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 11 h. After completion of the reaction, the mixture was passed through celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1.4 mL), and Boc_2O (170 mg, 0.78 mmol) was added to the solution. After stirring for 1 h, H_2O was added, and the resulting solution was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give compound **7** (262 mg, quant) as a pale-yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.90 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.34–7.08 (m, 3H), 6.97 (s, 1H), 5.25–5.22 (m, 1H), 5.12–5.10 (m, 1H), 4.68 (s, 1H), 3.64–3.54 (m, 2H), 1.45 (s, 18H). The spectrum was consistent with the reported data in reference 4.

ACKNOWLEDGEMENTS

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